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Chapter 22

# Vasoactive Substances and Inflammatory Factors in Progression of Liver Cirrhosis with Portal Hypertension

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## 1. Introduction

Portal hypertension (PH), a detrimental complication of many diseases, is abnormalities in pre-, intra- or post-hepatic portal venous system. Intrahepatic PH is the most common type, which is mainly cause by liver cirrhosis [1], liver cancer, and sometimes intrahepatic vascular abnormalities [2].

Hepatic venous pressure gradient (HVPG) is the difference between wedged hepatic venous pressure and infra vena cava pressure. PH is defined as an HVPG higher than 5 mmHg [3]. According to absence or presence of complications (splenomegaly and hypersplenism, esophageal varices and ascites), PH can be classified into compensated or decompensated phase. Meanwhile, an HVPG higher than 10 mmHg has been considered as a direct predictor of decompensation and a 10-year-follow-up study showed the significant worse long-term survival when HVPG $>$ 10 mmHg [4-6].

In cirrhotic PH, increased intrahepatic vascular resistance (IHVR) is the primary factor [7, 8] and subsequently increased portal vein inflow (PVI) worsens the situation of PH patients. This review will focus on the physiopathological changes happened in PH.

## 2. Correlation between vasoactive substances and IHVR/PVI

### 2.1. Nitric oxide

Nitric oxide (NO) is a potential vasodilator, produced by NO synthase (NOS). In a rat PH model induced by Thioacetamide, contraction of hepatic stellate cells, which resulting the

increase of intrahepatic vascular tone, was inhibited by incubated with nitroflurbiprofen *in vitro*, a nitric oxide-releasing cyclooxygenase inhibitor in a dose-dependent manner. In wild-type BDL mice, expression of NOS, especially eNOS was down-regulated [9]. Moreover, the significantly elevated total intrahepatic resistance was reduced significantly *in vivo* by the drug, indicating a potential role of NO on portal pressure [10]. In another rat PH model induced by bile-duct-ligation, intrahepatic vascular resistance increased significantly. Besides, relative level of phos-NOS decreased compared with sham group, leading to an inhibition of intrahepatic NO, although the relative mRNA level was increased [11]. Intrahepatic NO production is largely mediated by endothelial NO synthase (eNOS) and impaired when cirrhosis and secondary endothelial dysfunction existed, leading to the increase of intrahepatic vascular resistance. But the inhibition of NO might be the result of up-regulation of caveolin-1, a down-regulator of eNOS [12].

Contrastingly, extrahepatic NO is increased in PH patients. A clinical trial has shown that serum nitrate level was positively correlated with clinical presentation, (e.g. pulse rate, jaundice, hepatic encephalopathy, lower limb edema) and esophageal varices [13]. It is well established that NO results in dilation of splanchnic and systemic circulation as a powerful vasodilator and blood level of NO is increased as PH progresses [14-16]. Administration of CCl4 to eNOS(-/-) mice also led to an elevated NO production, which is eNOS independent [17]. Another study suggested that iNOS might be involved [18].

### 2.2. Carbon monoxide

Carbon monoxide (CO), a vasodilator producing by heme oxygenases (HOs) from heme [19], changes as HO-1 expression altered in PH patients [20, 21], which shares the same characters with NO [12]. Expression of intrahepatic HO-1 and -2 decreased in cirrhotic rats than that in normal ones. In situ perfusion with CO-releasing molecule-2, which leads to relaxation of hepatic stellate cells, and HO-1 inducer hemin could attenuated increased IHVR. ZnPP caused a higher IHVR attributing to inhibition of intrahepatic HO-1 in cirrhotic liver[22].

But things are different in splanchnic and systemic circulation. Reportedly, portal vein pressure (PVP) was significantly higher in bile-duct-ligated rats than that in sham group. Meanwhile, mRNA and protein level of HO-1 was also elevated significantly in lung [23].A clinical study has shown an activated HO/CO system in cirrhotic patients while the HO-1 activity and plasma level of CO were related with the severity of PH [20]. Arterial blood gas analysis showed an increase of COHb in bile-duct-ligated rats which could be reversed by ZnPP [23]. HO-1 could promote expression of VEGF and thereafter lead to formation of collateral vessels and higher splanchnic circulation [24].

### 2.3. Endothelin

Endothelin-1 (ET-1) is the most powerful vasoconstrictor in ETs family [25], which is primarily synthesized and acts in liver mainly in a paracrine fashion via ET A receptor causing vessel constriction [26]. In liver cirrhotic rats induced by carbon tetrachloride, both plasma

ET-1 level and PVP elevated dramatically while the mean hepatic tissue portal inflow reduced. And, perfusion with an antagonist of ET A receptor led to a reduction of plasma ET-1 level and PVP but did not improve the hepatic infusion suggesting that ET-1 was involved in development of PH [26]. It is consistent with a previous study which had demonstrated that liver blood inflow fluctuated in ET A and B receptors antagonist infusion groups and control group [27]. ET A and B receptors play different roles in CCl4-induced portal hypertensive rats. Antagonism of ET A or B receptor led to a reduced or increased of PVP and sinusoidal area in the cirrhotic rats respectively [28]. However, activation of ET B receptor leads to production of other vasoactive molecules, e.g. $TXA_2$ [29]. Besides, antagonism of ET A receptor alone cannot improve splanchnic circulation indicating ET B receptor plays a role on regulation in PH [30].

### 2.4. RAAS

It is well established that renin -angiotensin II (Ang II) -aldosterone -system (RAAS) plays an important role on body circulation. Ang II promotes proliferation and contraction of HSC and formation of collagen, leading to liver fibrosis [31]. In hepatorenal syndrome, a severe complication of cirrhotic portal hypertension with hyperdynamic circulation, systemic resistance, circulatory renin activity and plasma aldosterone were significantly increased [32]. Besides, angiotensin converting enzyme (ACE) and Ang II elevated in liver cirrhosis [33, 34]. Role of RAAS on portal pressure provides a new therapeutic alternative [35]. Animal model studies and clinical trials have shown that blockade of Ang II type 1 receptor (AT1R) significantly reduced portal perfusion pressure and HVPG [36-39]. ACE inhibitor also effects to reduce portal pressure in cirrhotic patients [40]. Inhibition of RAAS by losartan could also lead to a reduction of eNOS and ROS level in BDL rats [41].

### 2.5. Catecholamines

Catecholamines (CA) cause general physiological changes including increases in heart rate, blood pressure, blood glucose levels, and a general reaction of the sympathetic nervous system. In BDL cirrhotic rats, noradrenaline correlated with perfusion pressure dose-dependently, and this constrictive effect might be normalized by phentolamine but not propranolol, indicating that noradrenaline influences PVP through $\alpha$-receptor on portal-systemic collaterals [42]. In short-term PH induced by partial portal vein ligation (PVL), antagonism of phentolamine on $\alpha$-receptor was reduced; meanwhile, release of noradrenaline was down-regulated as NO up-regulated, indicating a potential role of CA, together with NO, on hyperhemodynamics and increased PVI [43]. Besides, expressions of tyrosine hydroxylase and dopamine β-hydroxylase were down-regulated in superior mesenteric artery revealing genetic regulation of adrenergic neurotransmitter system participating in the splanchnic vasodilation in PH [44]. Nevertheless, protein level of $\alpha$-receptor was higher in cirrhotic livers than in normal livers; activation of these $\alpha$-receptors located on HSC induced calcium spikes and HSC constriction through MAPK, NK-κB and AP-1 pathways, resulting in increased intrahepatic resistance [45]. When response to β-blockers was defined as a reduction $>$ 10% in HVPG from baseline, the proportion of non-responsers decreased, the rate of first-

bleeding among them increased and the diagnostic acuracy improved significantly contrasting with a 20% cut-off value.[46] Also, acute responsers to β-blockers have a better long-term outcome.[47]

### 2.6. Cannabinoid

Correlation between Cannabinoid and portal hypertension was paid attention in the last decades. Administration of anandamide, an endogenous cannabinoid, resulted in a drop of systemic circulation, mainly mean arterial pressure, although venous pressure changes verified, because of its effect on heart rate. Contrastingly, PVI and PVP increased in a dose-dependent fashion [48]. Treatment with antagonist of cannabinoid CB1 receptor in rats might lead to an elevation of blood pressure and a reduction of PVI and PVP, indicating cannabinoid is responsible for the dilation of systemic circulation [49]. It is in agreement with human. In cirrhotic patients, plasma level of cannabinoid was increased regardless of well-compensated or not [50]. But things are different in liver. Expression of CB1 receptor was dramatically down-regulated in both wild-type and eNOS knock-out group mice [9]. However, more researches are needed.

### 2.7. Cyclooxygenase, prostanoids and $TXA_2$

Activation of COX-2/prostanoid pathway promotes production of $TXA_2$ and $PGE_2$ [51]. In BDL rats, $TXB_2$, a stable metabolic of $TXA_2$ in isolated liver perfusate and PVP were increased in a time-dependent manner. Both inhibition of Kuffer cells and COX attenuate these changes. Further results indicated that COX-2 interact with Kuffer cells-derived $TXA_2$ was involved and its expression increased significantly [52]. Another group reported that COX-1 and PGI2 were responsible for decreased splanchnic resistance and increased PVI [53, 54]. However, elevated PVP of intrahepatic or pre-hepatic hypertension rats might be reduced by short- or long-term administration of COX inhibitor [18]. It is consistent with Graupera M et. al. [55]. In BDL portal hypertensive rats, elevated ET-1 interacted with Kuffer cells, increasing the responsiveness of p38MAPK through ET B receptor, activating $cPLA_2$ and promoting production of $TXA_2$, contributing to progression of portal hypertension [29].

### 2.8. Reactive oxygen species

Reactive oxygen species (ROS) is involved in many pathologic processes. In the case of PH, ROS level increases when circulatory NO decreases [56]. Administration of tempol, a type of superoxide dismutase, normalizes these changes with statistical significance in endothelial cells and cirrhotic liver, reduces intrahepatic vessel resistance and consequently increases PVI [57]. ROS also takes part in oxidative stress [58], lipid peroxidation, apoptosis and dysfunction of endothelial cells [41]. Reportedly, carvedilol, a β-blocker might ameliorate oxidative stress as well as inflammation and fibrosis in a CCl4-induced liver damage model, by reducing depletion of antioxidant enzyme, formation of collagen, and activation of NF-κB pathway, indicating a relationship between ROS and liver damage and fibrosis [59].

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## 3. Cytokines and liver fibrosis

Cytokine is a group of soluble protein or polypeptide, regulating immunologic response and hematopoiesis, participating inflammatory damage and repair. It consists of interleukins (IL), interferons (IFN), tumor necrosis factors (TNF), colony stimulating factors (CSF), chemokines, and growth factors. It has been reported that serum levels IL-6, TNF-$\alpha$ [60, 61], and IL-1$\beta$ [62] were elevated in hepatoportal sclerosis, and plasma IL-6 level was correlated with the deterioration of liver function [63]. Although IL-6 was increased, expression of IL-6 receptor in cirrhotic liver was decreased, leading to a reduction of hepatocyte response to IL-6, accompanied by an increase of gp130, indicating gp130 might be the potential negative regulator of liver IL-6 signal pathway [64]. In chronic patients with hepatitis C and/or schistosomal, plasma IL-4 level, as well as ROS, was increased and correlated with portal vein diameter, suggesting IL-4 might plays a role on PVI [65]. A clinical trial has shown that administration of probiotic led to a trend to reduction of plasma endotoxin, a mild but significant increase of TNF-$\alpha$ and a significant reduction of aldosterone [66]. Besides, increased PVP induced a up-regulation of $\alpha$-smooth muscle actin and collagen ◎ and ethanol exposure enhanced expression of TGF-$\beta$ and production of extracellular matrix via ERK1/2-JNK and p38MAPK pathway respectively, leading to fibrosis of liver [67]. Reportedly, IL-18 gene knock-out mice fed with methionine-choline-deficient diet (MCDD) showed significant exacerbated inflammation, revealing IL-18 was a negative regulator of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Tnf mRNA, but not il-6 or il-1b levelm was higher in db/db (Asc-/-) group than db/db (wt) group, indicating TNF-$\alpha$ expression drove the progression of non-alcoholic steatohepatitis [68]. In another type of liver cirrhosis caused by chronic infection of schistosomiasis, inflammation and following tissue repair led to obstruction of intrahepatic vessels and increased intrahepatic resistance. These defenses in liver was mediated by IL-10. But surprisingly, blockade of IL-10R resulted in an elevation of PH and a reduction of parasitic antigen specific B cells, but worsened pulmonary accumulation of eggs without an increase of PVP [69]. Co-infection of bacteria led to production of IL-17 [70]. Consistently, knock-out of IL-10, IL-12p40, and IL-13R$\alpha$2 contributed to a progressive and lethal liver fibrosis, showing the anti-fibrosis effects of these Th2-derived interleukins in schistosomiasis mansoni treated mice [71]. As demonstrated by Pinter M et. Al. [72], responders to sorafenib showed a decreased HVPG and VEGF, PDGF, PIGF, RhoA kinase, and TNF-$\alpha$ expression, revealed a potential effect of these growth factors and TNF-$\alpha$ on HVPG. And level of soluble TNF-$\alpha$ receptor in portal vein and hepatic vein was correlated with model for end-stage liver disease score, in accordance with previous studies [73]. However, intrahepatic TNF-$\alpha$, IL-1$\beta$, IL-4, and IL-10 were down-regulated while splanchnic levels were increased [74]. It is shown that IFN is involved in progression of hypertension, especially in viral infection- associated hepatitis [60, 75, 76]. Nowadays, IFN is usually used as antiviral treatment. Combination of 5-fluorouracil and IFN might reduce the portal hypertension related events [77]. Also, combination with IFN enhanced the viral clearance effect of ribavirin [78]. But IFN alone therapy only led to a temporary reduction of viral DNA load [79]. As documented, TGF-$\beta$ promotes liver

fibrosis in rats with biliary cirrhosis, cooperates with IFN-γ, IL-4, and TNF-α, etc [80]. More studies are needed to illustrate the detail effects of cytokines network on portal hypertension and liver fibrosis.

## 4. Molecules in further physiopathological progression

### 4.1. Splenomegaly and hypersplenism

Volume of spleen or splenomegaly in cirrhotic hypertension patients is primarily attributed to increased splanchnic circulation and congestion, in which vasoactive substances play important roles. And the main pathologic changes are lower counts of red blood cells, white blood cells, and platelets. Compared to normal spleen, lymphocytes in PH spleen were relatively reduced with a similar distribution; but total number of lymphocytes was increased due to the increase of spleen weight, with an elevated proliferation [81, 82]. MicroRNAome analysis showed that microRNA, expecially miR-615-3p was up-regulated in PH spleen significantly [83, 84]. It targeted on ligand-dependent nuclear receptor corepressor (LCoR), promoted the phagocytic capacity of macrophages through PPARγ pathway [84]. On the other hand, phagocytic capacity of macrophages might be inhibit by Phosphatidylinositol 3-kinase regulatory subunit 1 (PI3KR1) knock-down, accompanied by down-regulation of IL-1β and TNF-α [85]. Similarly, expressions of IL-1β and NALP3, a potential NF-κB activator participating in inflammation and immunologic response were up-regulated significantly in $CCl_4$-induced cirrhotic PH group compared to control group, together with typical splenomegaly histopathological changes [86]. In cirrhotic spleen, different from extrahepatic portal vein obstruction, thromopoietin (TPO) was reduced and this reduction is positively correlated with exacerbation of liver function, leading to a decrease of platelet counts [87].

### 4.2. Esophageal varices

Cirrhotic hypertension is characterized by hyperdynamic circulation and increased intrahepatic resistance as discussed before in this review. Splanchnic vasodilation results in increasing in HVPG. When HVPG is higher than 12 mmHg, risk of esophageal varices dramatically increased [88, 89]. Generally speaking, esophageal varices, as well as development of other collateral vessels, occur after HVPG and is followed by variceal bleeding [90]. Angiogenesis is associated with esophageal varices and portal hypertension, and expressions of VEGF are up-regulated, alone or together with TNF-α or PEGF[91-93]. Inhibition of VEGF/VEGF receptor pathway led to a decrease in hyperdynamic splanchnic circulation and collateral vessels [94]. Besides, metabolic disturbances occurred in cirrhotic PH lead to an elevation of glucagon [95]. The ratio of glycated albumin (GA) to glycated hemoglobin (HbA1c) was associated positively with the progression of liver cirrhosis, and patients with elevated GA/HbA1c ratio have severer esophageal variceal and higher risk of bleeding in HCV-related cirrhotic patients. This parameter might become a potential biomarker to predict the prognosis of these patients [96].

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### 4.3. Ascites

Portal hypertension in cirrhotic liver diseases is a main cause of ascites. As discussed before, vasoactive substances lead to an elevation of intrahepatic vessels resistance and a relative decrease of blood back-flow to liver. Besides, mechanisms below are involved: 1) hyperdynamic circulation. Hyperdynamic circulation is associated with disturbance of vasoactive substances. It is characterized by increased cardiac index and plasma volume and decreased systemic and splanchnic resistance [90]. 2) hypoalbuminemia following damage of liver function. One of the hyperalbuminemia occurred in cirrhotic PH is dysfunction of hepatocytes. In is shown that hypertension is a negative regulator to the number and structure of hepatocytes [97]. Poor blood supply induced by liver fibrosis and disturbance of hemodynamics results in intrahepatic hypoxia and damage of hepatocytes. Besides, primary liver diseases also cause inflammation and damage in liver. 3) renal function changes. This part will be discussed below.

### 4.4. Hepatorenal syndrome

It is well established that main cause of hepatorenal syndrome (HRS) is constriction of vessels in kidney induced by reduction of effective circulating blood volume (ECBV). As discussed previously, ECBV is reduced by systemic and splanchnic vasodilation induced by changes of NO, ET, PGs and $TXA_2$. Besides, some localized physiopathologic should be paid attention on. Expression of HO-1 in kidney was significantly reduced in BDL-induced cirrhotic rats [98]. Cyctatin C was increased in decompensated liver cirrhosis and HRS, thus it could be used as a predictor of HRS [99, 100]. Additionally, plasma level of ADAMTS13 was decreased and supplemental therapy might improve prognosis of patients with severe liver cirrhosis and HRS [101, 102].

### 4.5. Hepatic encephalopathy

Hepatic encephalopathy (HE) in portal hypertension is defined as C type HE. In PVL-induced PH rats, chemokine changes in splanchnic system, liver, and central nervous system (CNS) are different [103]. As reported, in CNS, CX3CL1/CX3CR1 and SDF1-$\alpha$/CXCR4 were increased. The former one promotes inflammation in CNS while the latter one modulates neuron activity through inhibitory neurotransmitters, e.g. gamma-amino butyric acid (GABA) [104]. ROS also participates in pre-hepatic portal hypertension [105, 106]. GABA level is also negatively regulated by dehydroepiandrosterone sulfate (DHEAS), which reduced in cirrhotic HE [107]. Besides, IL-6 has synergistic effect with ammonia in cirrotic HE patients [108]. Ammonia impairs brain eNOS activity, leading to significant abnormality of NO regulation and disturbance of blood supply [109]. Due to liver dysfunction in HE patients, elevated plasma manganese also indicates a bad prognosis [110].

## 5. Conclusion

Portal hypertension concerns a great number of molecules and complicated physiopathologic mechanisms. It can be classified into pre-, intra-, and post-hepatic PH according to the pri-

mary disease, with similar but not same involvement of molecules and mechanisms. However, we can still conclude that: 1) vasoactive substances play an important in systemic, splanchnic, hepatic, and even neurologic circulations which are closely related to blood supply, affecting the development, progression, and outcome of PH; 2) imbalance of pro-/anti-inflammatory cytokines lead to a systemic and/or localized regulation of signal pathways and modulate gene expression and silencing, cell proliferation and apoptosis, tissue damage and repair, and eventually life and death; 3) accumulating research advancements provide us new targets for treatment of PH, but it has a long way to go from bench to bedside.

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